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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,132	06/20/2003	Anthony P. Shuber	E0411.70037US00	4962

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/601,132	SHUBER, ANTHONY P.	
	Examiner	Art Unit	
	Sean E. Aeder	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8,10,11,13,14,17-21,23,24,27-30 and 32-34* is/are pending in the application.

4a) Of the above claim(s) *10,13,23,32 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-8, 11, 14, 17-21, 24, 27-30, and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/4/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/12/07 has been entered.

Claims 33-34 have been added by Applicant.

Claims 1, 4-8, 10, 11, 13, 14, 17-21, 23, 24, 27-30, and 32-34 are pending.

Claims 1, 14, 24 have been amended by Applicant.

Claims 10, 13, 23, and 32 were withdrawn and claim 34 is withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 1, 4-8, 11, 14, 17-21, 24, 27-30, and 33 are currently under consideration.

The following Office Action contains new rejections.

Rejections Withdrawn

All previously set-forth rejections are withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-8, 11, 14, and 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and dependent claims 4-8 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 1 is drawn to a method for screening a patient for the presence of colorectal cancer comprising performing a measurement and identifying the patient *as a candidate for additional cancer testing* if a measured amount is above a certain level; however, it is unclear what result indicates the *presence* of colorectal cancer. Essentially, the scope of the preamble (screening a patient for the presence of colorectal cancer) does not match the scope of the method steps (determining whether a patient is a candidate for additional testing). The omitted steps are: correlating a specific result to the presence of colorectal cancer in a patient.

Claim 14 and dependent claims 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 17 is drawn to a method for screening a patient for the presence of abnormal proliferating colorectal cancer cells comprising performing a measurement on a sample and *identifying a positive screen* as

a sample in which a measured amount is above a certain level; however, it is unclear what result indicates the *presence* of abnormal proliferating colorectal cells. Essentially, the scope of the preamble (screening a patient for the presence of abnormal proliferating colorectal cancer cells) does not match the scope of the method steps (identifying a positive screen). The omitted steps are: correlating a specific result to the presence of abnormal proliferating colorectal cancer cells.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24, 27-30, and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for diagnosing colorectal cancer in a patient comprising the steps of measuring a quantitative amount of genome equivalents of patient genomic DNA in a stool sample comprising shed cells or cell debris, wherein the quantitative amount of genome equivalents is measured by measuring an amount of fragments of less than 200bp; and if the amount of genome equivalents is above a predetermined threshold amount of genome equivalents, determining whether there is a statically significantly larger amount of nucleic acids greater than 200bp in length in said patient sample as compared to the amount of nucleic acids greater than 200bp in length in stool of a healthy subject wherein the presence of said significantly larger amount indicates the patient has colorectal cancer, the specification does not reasonably provide enablement for a method for diagnosing

every cancer in a patient comprising the steps of measuring a quantitative amount of genome equivalents of patient genomic DNA in a stool sample comprising shed cells or cell debris, wherein the quantitative amount of genome equivalents is measured by measuring an amount of fragments of less than 200bp; and if the amount of genome equivalents is above a predetermined threshold amount of genome equivalents, performing just any additional assay and obtaining just any result from said any additional assay to determine, in every way, if the patient has just any cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are drawn to a method for diagnosing every cancer in a patient comprising the steps of measuring a quantitative amount of genome equivalents of patient genomic DNA in a stool sample comprising shed cells or cell debris, wherein the quantitative amount of genome equivalents is measured by measuring an amount of fragments of less than 200bp; and if the amount of genome equivalents is above a

predetermined threshold amount of genome equivalents, performing just any additional assay and obtaining just any result from said any additional assay to determine, in every way, if the patient has just any cancer.

The specification teaches a method for diagnosing colorectal cancer in a patient comprising the steps of measuring a quantitative amount of genome equivalents of patient genomic DNA in a stool sample comprising shed cells or cell debris, wherein the quantitative amount of genome equivalents is measured by measuring an amount of fragments of less than 200bp; and if the amount of genome equivalents is above a predetermined threshold amount of genome equivalents, determining whether there is a statically significantly larger amount of nucleic acids greater than 200bp in length in said patient sample as compared to the amount of nucleic acids greater than 200bp in length in stool of a healthy subject wherein the presence of said significantly larger amount indicates the patient has colorectal cancer (see pages 12-16, in particular).

The state of the prior art dictates that if a particular assay is to be used to determine the presence of a particular cancer, a result from said assay must be identified in some way with said particular cancer. For instance, assays using a marker, such an amount of nucleic acids greater than 200bp in length, as a surrogate for a diseased state, must identify the presence of said marker with said diseased state. There must be some pattern that would allow the marker to predictably used in a diagnostic manner with success. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. Tockman et al teaches that

prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. Therefore, absent evidence of results from a particular assay correlating to a particular diseased state, one of skill in the art would not be able to predictably use said assay to detect said particular diseased state without undue experimentation.

The level of unpredictability that just any result from just any assay would detect just any cancer is quite high. Since neither the specification nor the prior art provide evidence of a universal association between the claimed method and every type of cancer, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method for diagnosing every cancer in a patient comprising the steps of measuring a quantitative amount of genome equivalents of patient genomic DNA in a stool sample comprising shed cells or cell debris, wherein the quantitative amount of genome equivalents is measured by

measuring an amount of fragments of less than 200bp; and if the amount of genome equivalents is above a predetermined threshold amount of genome equivalents, performing just any additional assay and obtaining just any result from said any additional assay to determine, in every way, if the patient has just any cancer, and Applicant has not enabled said method because it has not been shown that patient stool samples with a quantitative amount of genome equivalents above a predetermined threshold amount of genome equivalents and just any result from just any addition assay would predictably determine, in every way, whether said patient has just any cancer.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as broadly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 7, 11, 14, 17, 20, 24, 29, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loktionov et al (Clinical Cancer Research, February 1998,

4(2): 337-342) in view of Hromadnikova et al (BMC Pregnancy and Childbirth, 5/28/02, 2(4):1-5).

The claims comprise methods of detecting colorectal cancer comprising detecting genomic DNA in stool samples. It is noted that a method of "...measuring an amount of fragments of less than 200bp..." broady encompasses methods of measuring an amount consisting of fragments of less than 200bp and methods of measuring an amount comprising fragments of less than 200bp.

Loktionov et al teaches a method for diagnosing and screening a patient for the presence of colorectal cancer comprising measuring quantitative amounts of patient genomic DNA in a stool sample comprising shed cells or shed debris wherein the quantitative amounts are measured by measuring amounts of fragments of less than 200 bp. In fact, Loktionov et al teaches *two* methods of measuring said quantitative amounts: (1) detecting an amount of 113 bp fragments of patient genomic DNA in a stool sample comprising shed cells or shed debris to confirm DNA quality in order to identify a patient as a candidate for additional cancer testing if the amount is above a predetermined threshold amount, which would indicate a positive screen, before additional steps of diagnostic tests/examinations on the patient's stool sample for detecting the presence of colorectal cancer are performed (see Figure 1 and page 338 , in particular); and (2) detecting the presence of colorectal cancer by detecting a quantitative amount of genomic DNA (which would comprise fragments less than 200bp) in a stool sample comprising shed cells or shed debris by determining a 260:280 ratio (see Table 2 and Figure 2) in order to identify a patient as a candidate for

additional cancer testing if the amount is above a predetermined threshold amount, which would indicate a positive screen, before additional tests for detecting the presence of colorectal cancer are performed (see paragraph spanning pages 340-340, in particular). Loktionov et al further teaches, and one of skill in the art would recognize, that methods of screening for colorectal cancer are methods of screening for the presence of abnormal proliferating colorectal cancer cells (340, in particular).

Loktionov et al does not specifically teach that the genomic DNA amounts are measured in terms of "genome equivalents". However, these deficiencies are made up in the teachings of Hromadnikova et al.

Hromadnikova et al teaches a quantitative method of comparing amounts of DNA between samples comprising determining the number of "genome equivalents" and expressing amounts of DNA in terms of "genome equivalents" (page 2 right column, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to perform the method taught by Loktionov et al and express the measured amounts of patient DNA in the method taught by Loktionov et al in terms of genomic equivalents because expressing amounts of DNA in terms of genomic equivalents would be an effective way of normalizing data between multiple assays and Loktionov teaches that DNA of shed cells are what is actually being detected in order to diagnose colon cancer (page 340, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for expressing the measured amounts of DNA in the method taught by Loktionov in terms

of genomic equivalents because Hromadnikova et al teaches a quantitative method of comparing amounts of DNA between samples comprising determining the number of "genome equivalents" (page 2 right column, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 1, 4-8, 11, 14, 17-21, 24, 27-30, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loktionov et al (Clinical Cancer Research, February 1998, 4(2): 337-342) in view of Hromadnikova et al (BMC Pregnancy and Childbirth, 5/28/02, 2(4):1-5) as applied to claims 1, 4, 7, 11, 14, 17, 20, 24, 29, and 33 above, and further in view of Ahlquist et al (Gastroenterology, 2000, 119:1219-1227).

Anticipation of claims 1, 4, 7, 11, 14, 17, 20, 24, 29, and 33 by the combined teachings of Loktionov et al and Hromadnikova et al is described above.

The combined teachings of Loktionov et al and Hromadnikova et al do not specifically teach methods of detecting the presence of abnormal proliferating colorectal cancer cells / detecting colorectal cancer / diagnosing colorectal cancer by: (1) performing a DNA integrity assay; (2) detecting a ras mutation, or (3) performing a colonoscopy. However, these deficiencies are rendered obvious or made up in the teachings of Ahlquist et al.

Ahlquist et al teaches methods for screening a patient for the presence of colon cancer comprising measuring a quantitative amount of genomic DNA in a stool sample, and identifying the patient as a candidate for additional disease testing or identifying

patients with a positive screen if the amount of nucleic acid is above a predetermined threshold amount (pages 1221-1224, in particular). Ahlquist et al teaches colorectal cancer patients have higher fecal DNA yields than controls (page 1220 left column). Ahlquist et al further teaches methods of performing a DNA integrity assay (pages 1221-1222, in particular) and an assay to detect ras, p53, and BAT-26 mutations (page 12221 right column, in particular). Ahlquist et al further teaches colonoscopies as a means of detecting colon cancer (page 1219 right column, in particular). Ahlquist et al further teaches that fecal occult blood testing may detect cancers at an early stage; however, many cancers and most premalignant adenomas do not bleed and are missed (page 1219 right column, in particular). Thus, Ahlquist et al indicate that the sensitive and specific markers they teach would improve the effectiveness and efficiency of stool screening prior to colonoscopy (page 1219 right column, in particular).

Further, one of ordinary skill in the art at the time the invention was made would have been motivated to perform the method of detecting the presence of abnormal proliferating colorectal cancer cells / detecting colorectal cancer / diagnosing colorectal cancer taught by the combined teachings of Loktionov et al and Hromadnikova et al (described above) and perform the additional steps of performing a DNA integrity assay, an assay to detect ras mutations, and a colonoscopy taught by Ahlquist et al because Loktionov et al teaches the need for performing numerous assays to detect colorectal cancer (see paragraph spanning pages 340-341, in particular) and the assays taught by Ahlquist et al aid in the detection of colorectal cancer. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success

for perform the method taught by the combined teachings of Loktionov et al and Hromadnikova et al with a DNA integrity assay, an assay to detect ras mutations, and a colonoscopy because Ahlquist et al teaches performing a DNA integrity assay (pages 1221-1222, in particular), an assay to detect ras mutations (page 12221 right column, in particular), and a colonoscopy (page 1219 right column, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA